World Journal of Diabetes

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DOI: 10.4239/wjd.v6.i12.1223

World J Diabetes 2015 September 25; 6(12): 1223-1242
ISSN 1948-9358 (online)

REVIEW

Molecular and biochemical trajectories from diabetes to Alzheimer's disease: A critical appraisal

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Author contributions: Sandhir R and Gupta S contributed to this paper.

Conflict-of-interest statement: Authors have no conflict of interest.

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Received: May 6, 2015
Peer-review started: May 8, 2015
First decision: July 10, 2015
Revised: August 26, 2015
Accepted: September 7, 2015
Article in press: September 8, 2015
Published online: September 25, 2015

Abstract

Diabetes mellitus (DM), a metabolic disorder is a major orchestra influencing brain and behavioral responses *via* direct or indirect mechanisms. Many lines of evidence suggest that diabetic patients apparently face severe brain complications, but the story is far from being fully understood. Type 2 diabetes, an ever increasing epidemic and its chronic brain complications are implicated in the development of Alzheimer's disease (AD). Evidences from clinical and experimental studies suggest that insulin draws a clear trajectory from the peripheral system to the central nervous system. This review is a spot light on striking pathological, biochemical, molecular and behavioral commonalities of AD and DM. Incidence of cognitive decline in diabetic patients and diabetic symptoms in AD patients has brought the concept of brain diabetes to attention. Brain diabetes reflects insulin resistant brain state with oxidative stress, cognitive impairment, activation of various inflammatory cascade and mitochondrial vulnerability as a shared footprint of AD and DM. It has become extremely important for the investigators to understand the patho-physiology of brain complications in diabetes and put intensive pursuits for therapeutic interventions. Although, decades of research have yielded a range of molecules with potential beneficial effects, but they are yet to meet the expectations.

Key words: Diabetes mellitus; Alzheimer's disease; Insulin; Type 2 diabetes; Type 3 diabetes

Core tip: This review provides a synopsis in which a metabolic disturbance becomes indispensible for life and emerges as a molecular signal defect leading to a syndrome with multiple complications. Insulin is a spotlight player which draws a trajectory from diabetes to Alzheimer's disease with multiple divergence and convergence. We have discussed their interplay to speculate their shared molecular footprints. These biochemical and molecular commonalities provide a clue to the investigators to look inside a therapy with a common experimental and clinical platform and also provide an insight for new interventions as future perspective to find a potential stone to kill two birds together.

Sandhir R, Gupta S. Molecular and biochemical trajectories from diabetes to Alzheimer's disease: A critical appraisal. *World J Diabetes* 2015; 6(12): 1223-1242 Available from: URL: http://

www.wjgnet.com/1948-9358/full/v6/i12/1223.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i12.1223

INTRODUCTION

Every human cell relies on a complex set of programs installed during ontogeny. These programs and commands over them are the two interfaces which need faultless execution for normal body physiology. Physiology, behavior and defense are three eventful networks, which are supposed to function in synchronicity. A defect in any of these three events alters rest of two without any delay. Diabetes is a complex disorder where a molecular compromise alters the physiology with significant changes in behavioral responses.

Diabetes is associated with the production of auto-antibodies against pancreatic β-cells, *i.e.*, type 1 diabetes (T1D) or with insulin resistance (IR), *i.e.*, T2D[1,2]. T1D is a chronic hyperglycemic condition which affects multiple systems like brain, heart, eyes and kidneys[3]. Diabetes is found to be one of the causes of brain atrophy, mild cognitive impairment and white matter abnormalities[4-6]. In T2D insulin fails to stimulate utilization of glucose which gives rise to a phenomenon called IR. Chronic IR leads to several other complications such as lack of cellular energy, increased plasma lipids, cardiovascular problems and hypertension[7-11]. Increased risk of developing dementia and Alzheimer's disease (AD) was suggested in T2D, which was further supported by clinical and epidemiological studies[12,13]. Diabetes patients have two fold higher risk of AD as compare to non-diabetic patients[12]. In central nervous system (CNS), presence and distribution of insulin, insulin receptors (IRs) and its substrate are region specific[14,15]. Insulin is found to play important role in learning and memory by regulating the release of neurotransmitters and synaptic plasticity[16]. It is inferred from the literature that defective insulin signaling in diabetic patients plays a crucial role in synaptic physiology[17-19]. Many other molecules participating in insulin signaling pathway have been reported to be crucial for normal physiology[20]. Remarkable presence of IRs in different brain areas has provided a clue of possible link between insulin signaling and synaptic plasticity. This fact is strongly supported by up-regulation of IRs in hippocampus after training for spatial memory task *via* Morris-Water Maze[21].

In 1998, a possible link between insulin dysfunction and AD was established[22,23]. The postmortem AD brains showed reduced insulin like growth factor (IGF) mRNA levels and its receptor as compared to controls[24]. Impaired peripheral glucose sensitivity[25] and elevated plasma and cerebro-spinal fluid (CSF) levels of insulin[26-28] were also reported in AD patients. Thus, there are consistent reports showing involvement of impaired insulin signaling in cognitive decline in AD patients. The role of insulin in enhancing memory performance in AD patients was confirmed by rescuing effect of intravenous and intranasal insulin administration[29,30].

Attempts are being made to unscramble the cellular and molecular mechanisms connects diabetes and AD. Present review critically examines impaired insulin signaling in diabetes as well as in AD patients with emphasis on critical molecular players such as fork head box O-1 (FOXO1), mammalian target of rapamaycin (mTOR) and glycogen synthase kinase 3 beta (GSK3β) which can be potential therapeutic targets.

DIABETES MELLITUS

Diabetes mellitus (DM), a complex metabolic disorder is characterized by hyperglycemia with several macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy)[31]. Risk of developing any of microvascular complications of diabetes depends upon both the duration and the severity of hyperglycemia. Aldose reductase, initial enzyme in the intracellular polyol pathway is a key player involved in the development of diabetic complications. Polyol pathway converts glucose into sorbitol (glucose alcohol). Hyperglycemic condition increases the flux of glucose into this pathway and results in sorbitol accumulation which further leads to osmotic stress. Osmotic stress is reported to be most common underlying mechanism in the development of microvascular complications of diabetes[31]. American Diabetes Association has categorized diabetes as T1D and T2D. T1D is characterized by autoimmune destruction of pancreatic beta cells resulting in absolute absence of insulin whereas T2D is identified by peripheral IR. According to WHO reports 2012, 90% cases of diabetes are from T2D. Clinical and experimental studies suggested strong association between diabetes and cognitive impairment[32-35]. T2D is at the edge of several risk factors such as life style, obesity, physical inactivity, gestational diabetes history as well as genetic predispositions[36,37]. The hallmark symptoms of the disease are polyurea, polydipsia, polyphagia and weight loss[38]. Mechanisms of T2D involves lipid breakdown within fat cells, elevated plasma glucagon levels as well as an increase in electrolyte retention[39].

AD

AD is an age dependent neurodegenerative disorder associated with deposits of plaques and tangles in brain[40]. Only 1%-5% of the AD cases are found to have genetic differences and out of these cases, only 0.1% cases follow familial autosomal non-sex linked inheritance pattern[41]. AD was for the first time reported in 1906 by Alois Alzheimer, a German psychiatrist and pathologist as a progressive neurodegenerative disorder of memory loss and confusion[42]. Postmortem AD brains revealed intracellular accumulation of neurofibrillary tangles (NFTs) and extracellular deposition of amyloid

beta (Aβ) plaques as two major hallmarks of AD. NFTs are hyperphosphorylated form of tau protein, which are involved in microtubule dynamics while Aβ plaques are the cleavage product of amyloid precursor protein (APP) which is a transmembrane glycoprotein of unknown function. Mutation in three genes encoding APP, presenilin 1 (PSEN1) and presenilin 2 (PSEN2) contributes to genetic cases of AD[43]. These loci are responsible for the familial type of disease while environmental factors influence sporadic form of AD with unclear etiology. Mutated form of these genes increase production of Aβ-42 protein product, a major component of senile plaques. ε4 allele of the apolipoprotein E (APOEε4) is another risk factor for AD[44,45] which is thought to contribute in neuronal lipid homeostasis, repairs injured neurons, maintains synapto-dendritic connections and scavenges neurotoxins. Loss of cholinergic system is a major cause of cognitive deficit in AD patients and the current therapies are targeted at improving cholinergic functions[46].

TWIN MYSTERY OF AD AND DM: THE STORY SO FAR

In 1980, first line of evidence appeared when Adolfsson *et al*[47] performed glucose tolerance test on AD type dementia patients and hypothesized that hypoglycemic condition can ameliorate brain status. In 1994, Razay *et al*[48] spotted light on disturbed glucose metabolism and hyper-insulinemia in female AD patients and tried to establish a link between insulin dysfunction and dementia. In 1996, Messier *et al*[23] strengthened the evidences by uncovering the potential effects of glucose on memory and cognition of AD patients. In 2003, Messier[49] further established a clear association between non-insulin dependent diabetes mellitus with neuropathy which is an incidence of vascular disease and retinopathy, he further suggested that DM is a probable risk factor for AD. Many more groups stepped ahead to address the fundamental question of whether the basic premise about the disease is true or not.

In 2005, Susanne de la Monte's group at Brown University introduced the concept of brain diabetes or type 3 diabetes (T3D) and observed that after blocking brain insulin supply, neurons get disoriented and develops AD pathology in rats. This provided a promising platform to investigators to touch insight into T3D or brain diabetes[50]. In 2007, Li *et al*[50] published a review dedicated to common pathological process in AD and T2D which shared molecular degenerative cascades like dysfunction in insulin signaling pathway. In 2008, de la Monte *et al*[51] reappeared with some more set of explanations which were unclear in 2005. Diabetic brain was found to be compromised for acetylcholine homeostasis and cognitive impairment, whereas insulin sensitizers rescued these effects[52]. In 2009, Gotz *et al*[52] described the molecular commonalities between T2D and AD with hallmark feature of amylin deposition in pancreatic islets of T2D patients, whereas Aβ and NFTs deposition in AD brain which are characteristic fibrillar proteins leading to cell loss. In 2010, Saini *et al*[53] contributed a relevant publication to World Journal of Diabetes, establishing a molecular mechanism of IR in T2D. Crucial molecular players in these pathways came into the picture and provided new therapeutic targets. In 2011, Park[54] suggested that pathogenic alterations in insulin signaling, Aβ aggregation, oxidative stress, inflammation and glucose metabloism contributes to AD as well as DM. Streptozotocin induced diabetic rat model showed co-appearance of tau hyperphosphorylation and cognitive decline as an interesting evidence[55]. On the basis of clinical and biochemical evidences, it was further suggested that both of these diseases promote each other's progression[56]. It has recently been found that proinflammatory signals in the brain impair insulin signaling, mitochondrial dysfunction, synaptic crosstalk as well as cognitive impairment[57].

Since 1980, many reports appeared in literature to describe the correlation between these two distinct problems with common molecular and cellular interface. Glucose metabolism and insulin signaling are major elements bridging AD and diabetes. Some relevant reports, unraveling the twin mystery of AD and DM are listed in Table 1.

THE CHICKEN OR EGG QUESTION

In spite of so many striking evidences, due to common interface of homeostatic mechanisms of AD and DM, the chicken or the egg question has remained unresolved. Citing all relevant findings, in 2005, first time Suzanne de la Monte has introduced insulin signaling dysfunction as a core of AD. To untangle this mystery, evidence of crosstalk between AD and DM, were put forward as crucial milestones. Patients with T2D were found to be at high risk of developing mild cognitive impairment (MCI), dementia and AD[60,61]. Similar type of evidence for MCI, dementia and AD were found in experimental models of diabetes[56,62-65]. AD brains have similar pathogenesis as observed during insulin deficiency[24,66-68]. Studies with AD patients and animal model of AD showed that intranasal insulin therapy significantly improved cognitive performance[69-71]. These clinical and experimental studies suggested that both of these disorders share common biochemical and molecular cascades[60,72,73]. Some of these common bridging elements have been schematically represented in Figure 1. Interestingly, insulin has been found to regulate Aβ and tau metabolism, which are major hallmarks of AD[74,75]. It is also evident that in T2D patients insulin signaling dysfunction accelerates AβPP (amyloid beta precursor proten)/Aβ trafficking from trans-Golgi network, a major site for Aβ generation and alters dynamicity of a Aβ synthesis[75]. Some studies report the presence of some downstream regulators of insulin signaling pathway which are involved in cleavage of AβPP at γ-secretase site, a determining site for Aβ

Table 1 Relevant reports bridging Alzheimer's disease and diabetes mellitus

Ref.	Key findings
Adolfsson *et al*[47]	Hypoglycemic condition can ameliorate brain status in AD
Razay *et al*[48]	Disturbances in glucose metabolism and hyper-insulinemia in female AD patients are responsible for cognitive decline
Ruigómez *et al*[58]	Documented a relationship between non-insulin dependent diabetes and neuropathy
Li *et al*[50]	Defective insulin signaling is a shared degenerative cascade in disease pathology of both AD and DM
Ke *et al*[59]	Amylin deposition in pancreatic islets of T2D patients whereas, Aβ and NFTs deposition in AD brain are common hallmarks feature of diabetes and Alzheimer's in terms of protein deposition
Saini[53]	Elucidated cellular and molecular mechanisms of insulin resistance and provided understanding for the molecular therapeutic targets
Park[54]	T2D and AD have some common pathogenic alterations like defects in insulin signaling, Aβ clearance, glucose metabolism, O-GlcNAcylation, Aβ aggregation by AGEs, inflammation, oxidative stress and circulating cortisol levels
Correia *et al*[55]	Amyloidogenesis and mitochondrial dysfunction are common denominators potentiating brain dysfunctions
Talbot *et al*[57]	Brain insulin signaling pathway including IGF-1R → IRs-2 → PI3K signaling is directly involved in AD and thus one of a causal factor in disease pathogenesis

AD: Alzheimer's disease; DM: Diabetes mellitus; T2D: Type 2 diabetes; NFTs: Neurofibrillary tangles; Aβ: Amyloid beta; AGEs: Advanced glycation end products; IGF-1: Insulin like growth factor-1; IRs: Insulin receptors; PI3K: Phosphatidylinositide 3-kinases.

Table 2 Symptoms of Alzheimer's disease symptoms in diabetes mellitus patients and symptoms of diabetes mellitus in Alzheimer's disease patients

Ref.	Key findings
Gasparini *et al*[75]	In T2D patients insulin metabolism dysfunction accelerates AβPP/Aβ trafficking from trans-Golgi network, a major site for a Aβ generation
Phiel *et al*[76]	Some studies claim for the presence of downstream regulators of insulin signaling pathway which are involved in cleavage of AβPP at gamma-secretase site, a determining site for Aβ amyloidogenicity
Steen *et al*[24]	Extensive dysfunction of IGF-I and IGF II signaling mechanisms reported in AD brain
Rivera *et al*[66]	Insulin and *IGF* gene expression altered with abnormal receptor binding in AD brain

AD: Alzheimer's disease; T2D: Type 2 diabetes; Aβ: Amyloid beta; IGF: Insulin like growth factor.

amyloidogenicity[76]. Although, investigators found many evidences of common features in both of these disorders, the chicken or the egg question is still valid and needs parsimonious explanations. Key reports supporting AD like symptoms in DM patients and DM like symptoms in AD patients are listed in Table 2.

AMYLOIDOGENESIS: A COMMON PATHOLOGY IN AD AND DM

Protein structure and function is crucial for maintenance of life, moreover its mishandling leads to diverse pathological conditions. Neurodegenerative disorders lie in a class of disorders associated with different types of abnormal fibrous, extracellular poteinaceous deposits which are referred as amyloid[77]. β-sheet structured insoluble moieties play an important role in the pathology of many protein misfolding diseases[77]. Globular proteins due to their tertiary structure constrain, undergo destabilization of their native structure and adopt partial folded and unfolded form while natively folded proteins are devoid of any ordered form so they passes through the stabilization process of fibrillogenesis and acquire a partially folded conformation[78]. In a crowded cellular milieu when functional protein erroneously interacts with other components and transforms itself into ordered stable form, the phenomenon is known as amyloidogenesis.

Interestingly AD and DM both involve amyloidogenesis. Extracellular deposition of Aβ plaques is a feature of AD while amyloidogenic peptide deposition in pancreatic islets of Langerhans is a characteristic feature of T2D[79,80]. Amyloid deposits in islets consist of 37 amino acid peptide referred to as islet amyloid polypeptide (IAPP) amylin[81,82]. Aβ and IAPP have same folding patterns and configuration[83]. IAPP is reported to generate islet β-cells toxicity in the same way as Aβ do in neurons. Although we are far to understand the exact mechanism of amyloid formation, it can be speculated from the emerging data that amyloid formation is a basic cause of AD, DM and other disorders related to protein deposition[84-86].

IR AS COMMON METABOLIC COMPROMISE IN AD AND DM

Glucose is the only required source of energy for neurons and any disruption in glucose metabolism leads to compromised neuronal functions[39]. Presence of insulin is crucial for brain in terms of its peculiar CNS functions[87] but any disturbance in its physiological level leads to CNS dysfunction. IRs are reported with low binding affinity with insulin in postmortem AD brain[87,88]. Moreover many other insulin signaling markers were altered in AD brain[24]. Elevated insulin plasma level in AD patients indicates a closed association of AD and IR[26,28]. Animal model studies revealed that factors contributing to T2D also regulate Aβ dynamics[89].

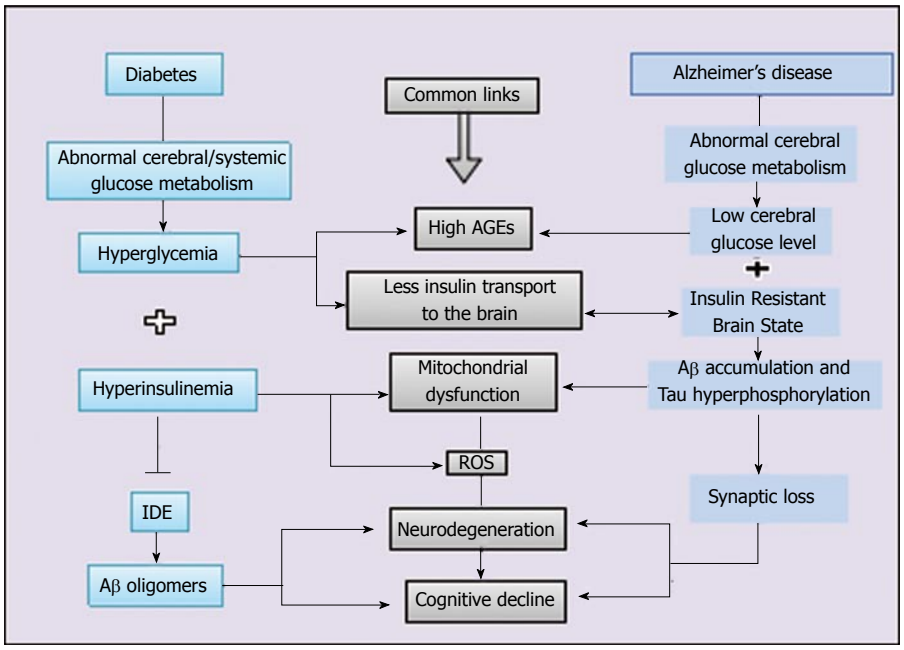

Figure 1 Schematic representation of commonalities between diabetes and Alzheimer's disease. Hyperglycemia and hyperinsulinemia are hallmark features of diabetes which leads to advanced glycation end product, reduced insulin supply to brain as well as mitochondrial dysfunction, which further leads to vicious cycle of oxidative stress. On the other side, any defect in glucose metabolism and insulin signaling in brain is one metabolic status of Alzheimer's disease brain which translates into insulin resistant brain status and converges to all common interfaces of mitochondrial dysfunction, oxidative stress and neurodegenrtaion. IDE: Insulin degrading enzyme; Aβ: Amyloid beta; AGEs: Advanced glycation end products; ROS: Reactive oxygen species.

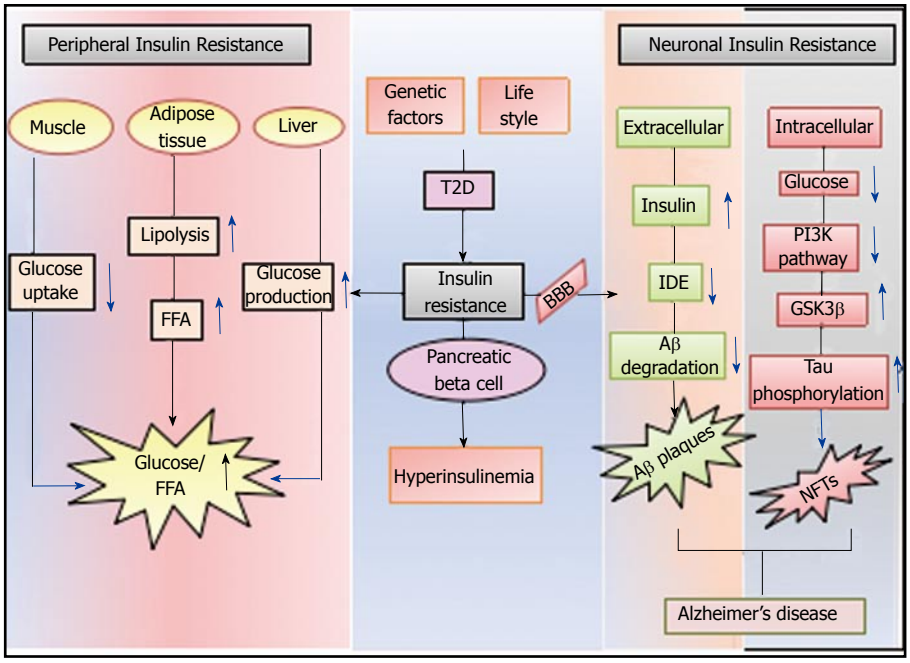

Figure 2 Diagrammatic representation of peripheral and neuronal complications of insulin resistance in case of type 2 diabetes. Insulin signaling dysfunction in peripheral system affect muscle, adipose tissue and liver (by decreasing glucose uptake, increasing free fatty acids) and by increasing glucose production respectively. When this dysfunction appears in CNS as a diabetes complication (by limited insulin supply to brain), it leads to deposition of Aβ plaques and NFTs in extracellular and intracellular milieu of neurons respectively and represents AD type brain status. AD: Alzheimer's disease; T2D: Type 2 diabetes; IDE: Insulin degrading enzyme; PI3K: Phosphoinositide 3-kinase; Aβ: Amyloid beta; NFTs: Neurofibrillary tangles; GSK3β: Glycogen synthase kinase 3 beta; FFA: Free fatty acids; BBB: Blood brain barrier.

With this set of data it is clearly understood that IR or impaired IRs not only typify T2D but also orchestrate AD. Figure 2 depicts that how IR bridges peripheral and neuronal IR and leads to AD.

How insulin modulates brain functions?

Insulin expression in brain remained a debated topic for investigators and raised a question on its significance at ectopic site. Brain synthesizes insulin locally as well

as receives through the blood brain barrier (BBB) mediated transfer[90]. With curious attempts, scientists documented its role in feeding behavior and energy homeostasis which integrate whole body physiology[91]. The first article unpinning the relation between brain and insulin was reported in 1960, in which intracisternal injection of insulin in dogs reduced glucose levels, both in CSF and blood with its direct effects on the parasympathetic area of the brainstem[92]. Later, brain-centered glucoregulatory system (BCGS) that is involved in maintenance of blood glucose levels was found to act *via* insulin dependent as well as independent mechanisms[93]. The hypothesis of BCGS and its crosstalk with pancreatic islets gained experimental momentum by multiple supporting evidences that provided a clear understanding of BCGS[93]. BCGS is recognized as mechanistic node present in CNS which is channeled through peripheral hormone status[93]. Both of these regulatory nodes co-operate with each other and compensate the load of other's failure but when both are compromised, DM is an unavoidable issue.

Insulin as a synapto-dendritic player

Insulin has drawn a wide trajectory in brain molecular milieu from cognitive function to orchestrate functions like development of neurite outgrowth, modulation of catecholamine release and uptake, regulation and trafficking of ligand-gated ion channels, expression and localization gamma-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, synaptic plasticity regulation *via* NMDA, Phosphoinositide 3-kinase-Akt (PI3K-Akt)[94] and maintenance of excitatory synapses[95].

Presence of IRs at synapses rich in plasticity (hippocampus and cortex) reveals its involvement in cognition[90]. This fact was further strengthened in 1999 when Zhao *et al*[21] reported that rat hippocampus IRs expression is up-regulated when they are subjected to spatial memory task in Morris water maze. IRs are enriched in synaptosomes[96], co-localizes with axon terminal markers synaptophysin, synapsin, *etc*.[97], and dominates in post-synaptic density (PSD) fractions to interact with scaffolding protein shank and PSD-95. Insulin is also involved in various neuromodulatory functions such as electrophysiological properties of neurons[98,99], neurotransmitter receptors[100,101], trafficking of ion channels[102], neurotrophic effects[103,104] and the neuroprotective role against a wide range of insults such as apoptosis[105], oxidative stress[106], β-amyloid toxicity[107] and ischemia[108] in animal models as well as human studies.

Hyperinsulinemia is reported to reduce cholinergic activity in mice brain and resulted in impaired retention of an inhibitory avoidance[109]. It also alters membrane potential to affect the ion transport[110,111]. In streptozotocin induced rat model of DM, long term memory potentiation was found to be impaired and insulin treatment rescued the effects[112-114]. With these set of potential findings, it is evident that insulin is crucial synapto-dendritic player altering dendritic arbor morphology as well physiology.

INSULIN RECEPTORS PLAYING DOWNSTREAM MOLECULAR ORCHESTRA: INSIGHT INTO THE MECHANISMS

Investigators unraveled the IRs downstream molecular orchestra and speculated that IRs activation further activates PI3K/protein kinase B (PI3K/PKB) pathway[115]. GSK3β is a major player of this pathway and involved in long term potentiation/long term depression (LTP/LTD) which is a sole mechanism of memory formation and synaptic plasticity[116]. Other than insulin, PI3K can be activated by multiple growth factor ligands including nerve growth factor, brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), insulin like growth factor-1 (IGF-1)[117].

After investigating for over two decades, it is safe to accept that PI3K/Akt signaling pathway is a potential window through which various ON/OFF switches of cognitive decline get operated. Protein kinase B (PKB), also known as Akt is a main downstream hub of various other pathways and exists with its widely expressed isoforms such as PKB-α, PKB-β and PKB-γ (predominates in CNS)[118]. Akt pathway has its regulating arms over neuronal survival, glucose uptake, angiogenesis, metabolism and proliferation[119]. Moreover Akt has a negative feedback regulation over these *via* phosphatase and tensin homolog, protein phosphatase 2A, c-jun N-terminal kinases (JNK) and forkhead box O (FOXO)[119].

Loss of PI3K control is a central mechanism of neurodegeneration in DM patients[120]. Moreover, AD patients are reported with sustained PI3K/AKT signaling which is a primary response linking insulin, IGF resistance, tau pathogenesis and synaptic decline[121]. GSK3, mammalian target of rapamycin (mTOR) and FOXO are three main downstream targets playing this whole orchestra (represented in Figure 3).

Glycogen synthase kinase3β, a pivotal kinase in AD and diabetes

Extensive reports supporting pivotal role of GSK3β proposed "GSK3β hypothesis of AD"[107], according to which GSK3β over-expression leads to impaired memory, amyloid β accumulation, tau hyperphosphorylation, neuronal defects and microglial mediated inflammation cascades. Genetic studies established that insulin signaling genes are also loci of AD[106]. Cholinergic system is one of the major regulating knob under GSK3β control with choline acetyltransferase and acetylcholinesterase as regulating keys[107,108]. GSK3β leads to reduction of acetylcholine synthesis, which is in accordance with the cholinergic deficit observed in AD

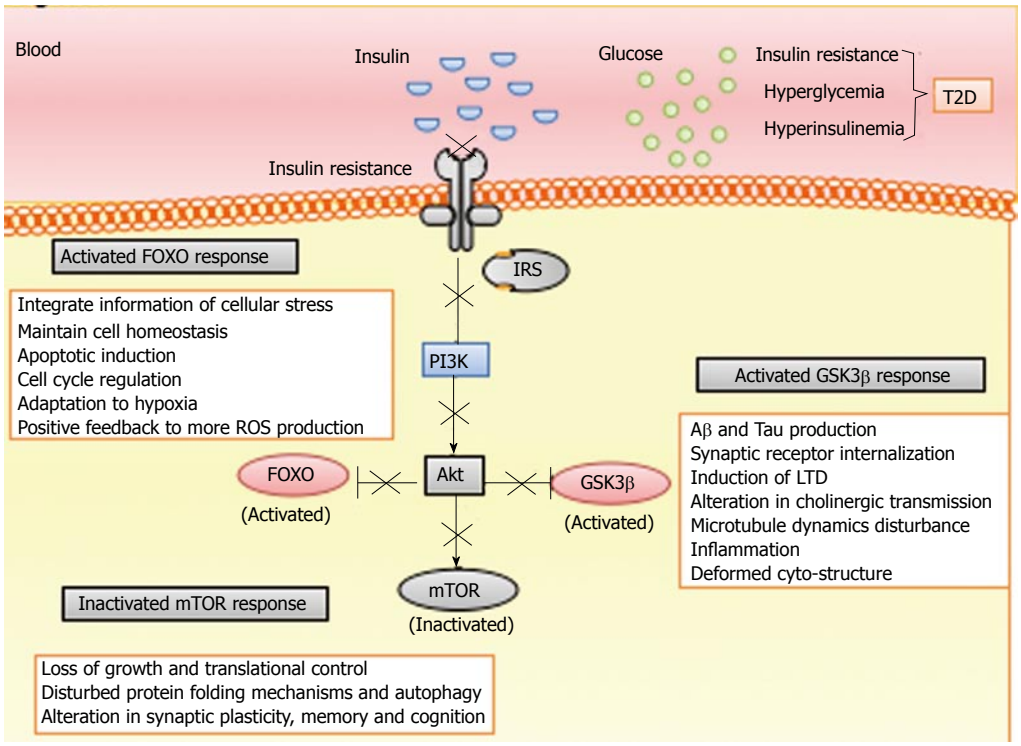

Figure 3 Diagrammatic representation of molecular orchestra downstream of insulin receptor. IRs activation leads to downstream PI3K signaling pathway with Akt as a central hub which diverges into three main branches including FOXO, GSK3β and mTOR. Akt inhibition leads to activated FOXO and GSK3β response while inactivated mTOR response. FOXO activation leads to cellular stress response, mTOR dysfunction leads to loss of translational control and altered cognition while GSK3β activation leads to Aβ and tau production. T2D: Type 2 diabetes; PI3K: Phosphatidylinositide 3-kinases; Aβ: Amyloid beta; GSK3β: Glycogen synthase kinase 3 beta; FOXO: Forkhead box O; mTOR: Mammalian target of rapamycin; LTD: Long term depression.

brain[122]. GSK3β negatively affects axonal transport, microtubule dynamics and destabilizes microtubule by lowering its affinity with GSK3β phosphorylated tau[95-97] and contributes to AD pathology. Being a key mediator of apoptosis it may directly contribute to neuronal loss in AD[105,123]. GSK3β interestingly controls cell cycle in two way system by activating intrinsic pathway to trigger cell death and by inhibiting death receptors by extrinsic pathway[124]. In 2002, Sun *et al*[125] and in 2003, Phiel *et al*[76] reported that GSK3β increases Aβ production by regulating APP cleavage. On exposure of Aβ, neurons inhibit PI3K pathway and increase GSK3β activity[126]. GSK3α as well as GSK3β both are found to be an inducer of tau phosphorylation[127-132]. Drastic alteration in dendritic arbor and post synaptic density, a common morphological feature of AD brain has been observed in GSK3β deficient mice[132]. GSK3β is the only kinase involved in NMDAR-LTD[124]. It also maintains a threshold of LTP and LTD, *i.e.*, maintenance of metaplasticity[116,133,134]. Modulation in regulated/constituted expression of GSK3β orchestrates neuronal plasticity[84,116,134-140]. GSK3β dramatically induces the internalization of AMPA and NMDA receptors[141,142] and decreases the level of PSD proteins, a molecular marker of memory acquisition[77]. GSK3β phosphorylates CREB protein to inhibit its function which is a universal modulator of memory. It aids in cyto-architecture of cell by promoting actin and tubulin assembly for synaptic reorganization[143]. GSK3β is also a pivotal kinase involved in adult hippocampal neurogenesis which negatively regulates it by reducing the number of proliferating neurons in the dentate gyrus region[144,145]. GSK3β is directly involved in the production of pro-inflammatory cytokines such as interleukin (IL) 6, IL-1β, TNF-α which indicates its positive regulation towards inflammatory mechanisms[146,147].

FOXO1 signaling: A mechanistic node for a vicious cycle of IR and Aβ up-regulation

FOXO1 signaling is a mechanistic node and regulates the fine balance of oxidative stress pathways (depicted in Figure 4). Before moving into the mechanism part, it has been briefly discussed about the dramatic story of its evolution in molecular series under discovery[148]. Many lines of evidence suggest its role in AD as well as IR with major involvement in cell proliferation, differentiation, cell survival, apoptosis and development of proliferative late onset diseases[148]. Short term activation of this player leads to protective mechanism of scavenging reactive oxygen species (ROS) which is a part of normal cell physiology but its persistent activation awakes the apoptosis pathway[148]. Cellular milieu tends to maintain a balance oxidant and antioxidants concentration to cope up any environmental stress, but whenever this balance acquires any plane of inclination, it comes to the cell survival[148].

Wnt and β catenin up-regulate FOXO signaling *via*

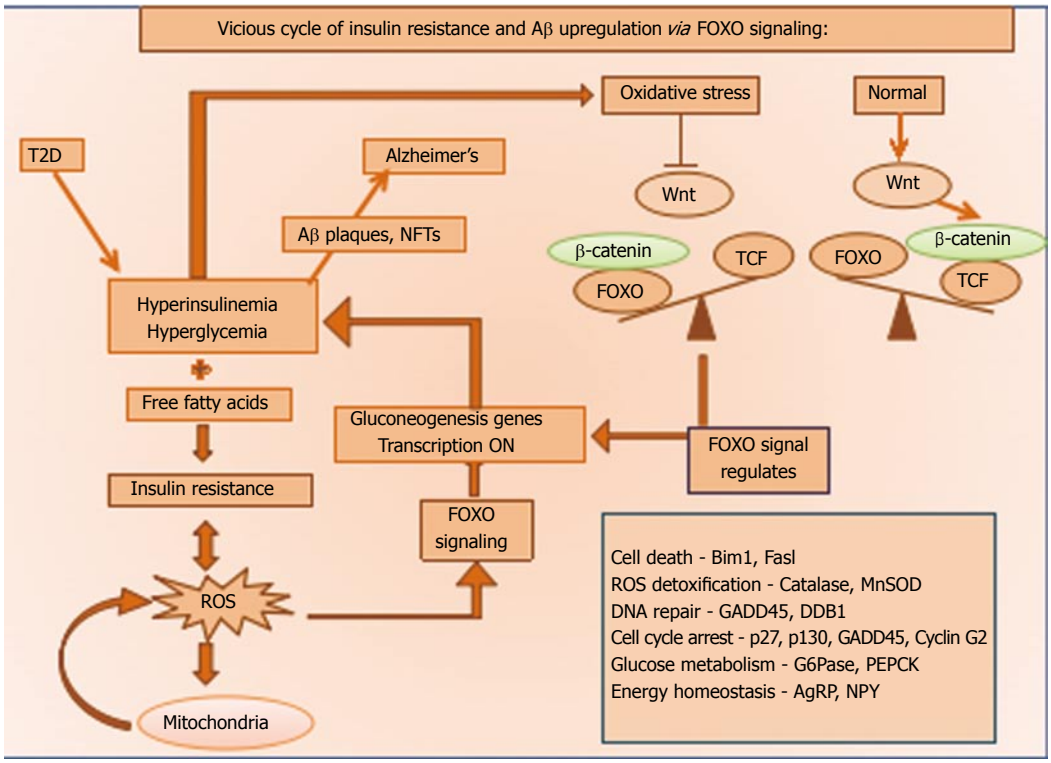

Figure 4 Diagrammatic representation of vicious cycle of insulin resistance and amyloid beta up regulation *via* forkhead box O signaling. FOXO signaling is a protective mechanism adopted by body to cope up with any cellular stress by ROS detoxification. In case of DM whenever there is any metabolic disturbance like hyperinsulinemia and hyperglycemia, it leads to further oxidative stress and ROS generation which promotes further trigger for FOXO signaling and promotes a vicious cycle of ROS generation leading the cell towards apoptosis. T2D: Type 2 diabetes; Aβ: Amyloid beta; FOXO: Forkhead box O; ROS: Reactive oxygen species; TCF: T cell factor; DM: Diabetes mellitus.

oxidative stress pathways[148]. Wnt signaling inhibits GSK3β expression and mediates β catenin transport into the nucleus and modulates transcription of T cell factor family gene, which has function opposite to FOXO1, this is known as the canonical pathway of Wnt signaling and involved in lipid and glucose metabolism[149]. ROS production inhibits canonical pathway of Wnt signaling and guides β catenin towards FOXO which acts as a cofactor of FOXO and enhance its transcription. Foxo signaling promotes gluconeogenesis and leads to hyperglycemia and hyperinsulinemia which further increases NFTs and Aβ accumulation to gear up ROS production and drives the vicious cycle of Oxidative stress[150].

When insulin is absent, FOXO1 is located in the nucleus and promotes transcription of respective enzymes for hepatic glucose production while in the presence of insulin; PKB is activated and leads to nuclear exclusion of FOXO 1 by phosphorylating it. State of IR in case of DM leads to impairment of PKB pathway and inhibition of FOXO activity resulting in hepatic glucose production triggering a vicious cycle of hyperglycemia and oxidative stress. FOXO, the downstream activator of PI3K/AKT controls energy homeostasis, locomotor behavior and leptin sensitivity[151,152].

mTOR pathway: A crucial intersection of AD and DM

mTOR pathway has been evolved as environment sensor and growth promoter in unicellular organisms but as multi-cellularity emerged it acquired its role in central growth and homeostasis mechanisms. Metabolism and cell growth are two basic requirements and their proper functioning depends upon each other. Since mTOR pathway is centered for growth processes, it is activated by nutrition as well as insulin[136]. In evolutionary history from yeast to rodents, mTOR has evolved as key modulator of aging. Many investigators attempted to understand its basic role and decades of extensive pursuit revealed extensive network of mTOR. mTOR is found to accelerate growth but it has compromised some of metabolic signals by conflicting pathways and introduced a paradox or better to say insulin paradox[137].

This paradox appeared from the evidences of compromised insulin signaling with good health and IR leading to compromised health while both of the cases are of poor insulin signaling[138]. Parsimonious explanations are, compromised insulin signaling is unable to activate mTOR (good for health) while IR may be due to hyperactive mTOR which is bad. So in previous case compromised insulin signaling inhibits mTOR insurgence while active mTOR is promoting IR in the later case[138]. Mechanistic node of this story, S6 kinase (S6K) is activated by mTOR to phosphorylate and degrade insulin receptor substrate-1 (IRS-1) which ultimately leads to insulin desensitization[139,140].

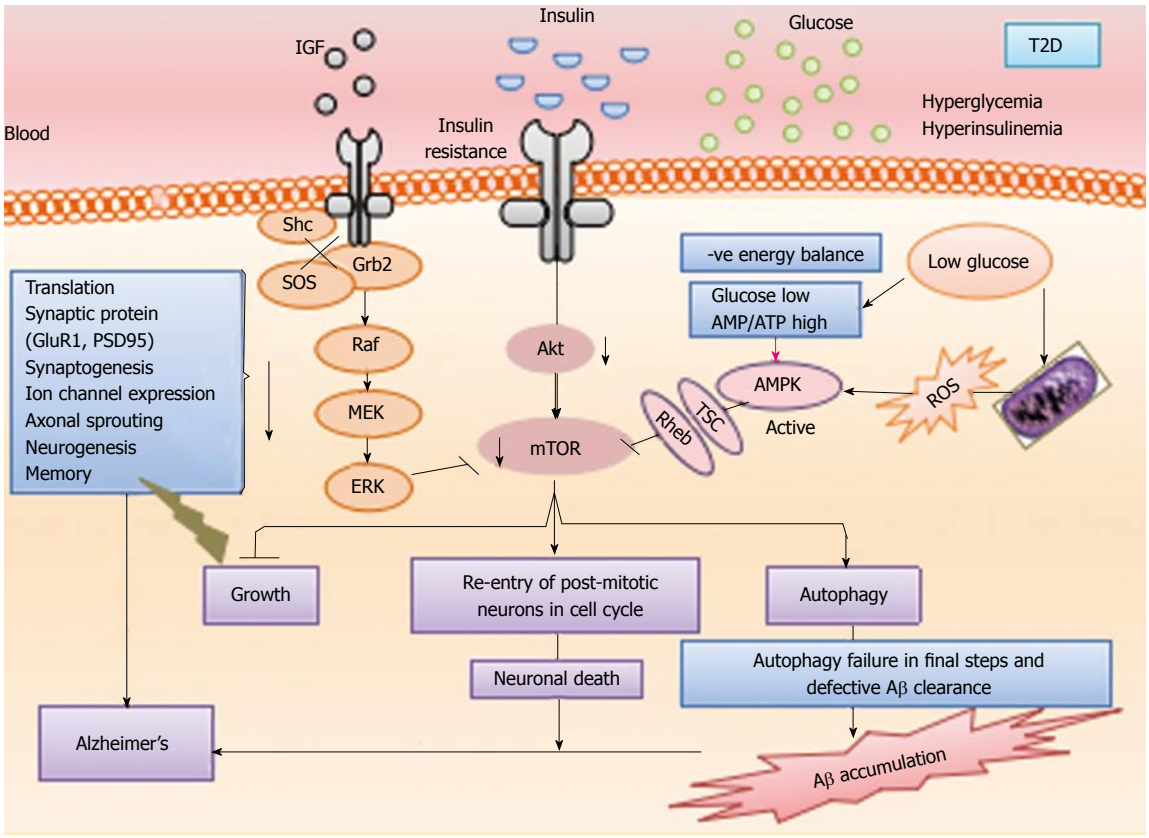

Figure 5 Diagrammatic representation of mammalian target of rapamycin pathway: A crucial intersection of type 2 diabetes and Alzheimer's disease. Diabetes results in dysfunctional insulin signaling which brings mTOR pathway down and ultimately results in autophagy failure to accumulate Aβ, inhibit re-entry of post mitotic neurons in cell cycle, stimulate aberrant growth pathways, lose of translational control and impaired neurogenesis, *etc*. T2D: Type 2 diabetes; IGF: Insulin like growth factor; mTOR: Mammalian target of rapamycin; Aβ: Amyloid beta; ROS: Reactive oxygen species.

mTOR signaling has a dramatic interplay with Aβ and tau proteins which are two hallmarks of AD in their aggregated forms. It was reported in 2012 that Aβ is an activator of PI3K/Akt pathway which further switches on mTOR cascade[153]. *In vitro* studies suggest that Aβ application elevates the level of p70S6K, a downstream target of mTOR which contributes in development of NFTs[154,155]. Consistent *in vitro* reports validated the fact that mTOR activity and activated p70S6K are either cause or consequence of the molecular cascade and hence are found with elevated levels in hippocampus and cortex of animal model of AD[156,157]. mTOR suppression leads to induction of autophagy which is a cell cleaning process. In AD brain it is evident that neuronal autophagy is induced to end up with impaired steps and leads to massive accumulation of Aβ plaques[158].

mTOR has characteristic property of maintenance of protein homeostasis, translational control and cellular maintenance, which plays an important role in the maintenance of synaptic plasticity. Figure 5 provides detailed information of mTOR domain. To execute these entire tasks mTOR pathway is operated under fine control of several surface receptors such as NMDA, dopaminergic and metabotropic glutamate receptors (mGluRs) and BDNF[159-163]. mTORC1 is one of the downstream targets of PI3K/AKT pathway which is very important for synaptic plasticity, neuronal repair, protein folding mechanism and autophagy[164,165].

INFLAMMATION: A COMMON ALARM FOR AD AND DM

Inflammation is an exceedingly complex but equally fascinating and costly host defense system evolved with proximate set of mechanisms and exhibit phenotypic plasticity. It is crucial for life but once dysregulated, it can be detrimental. Emerging field of metabolic and aging syndromes spurred a renewed interest of scientists into inflammatory mechanisms. This is a compensatory mechanism for body to cope up with the hostile environment which involves many subtle factors and specialized cells to fight against any threat[166]. It has very critical progressive role with analogous mechanism in diabetic patients showing IR and defective neuronal signaling in AD patients[167]. Thus, DM and AD share inflammation as a common pathological feature.

Studies have reported elevated levels of proinflammatory cytokines such as TNF-α, IL-6, IL-1β, *etc.*, in AD patients[168]. In diabetes patients, elevated TNF-α triggers various stress kinases to phosphorylate IRS-1 (at inhibitory serine residues) and disrupts insulin signaling[169-171] (explained in Figure 6), while blocking TNF-α rescues its effects in obese mouse model[172,173]. JNK and double-stranded RNA-dependent protein kinase

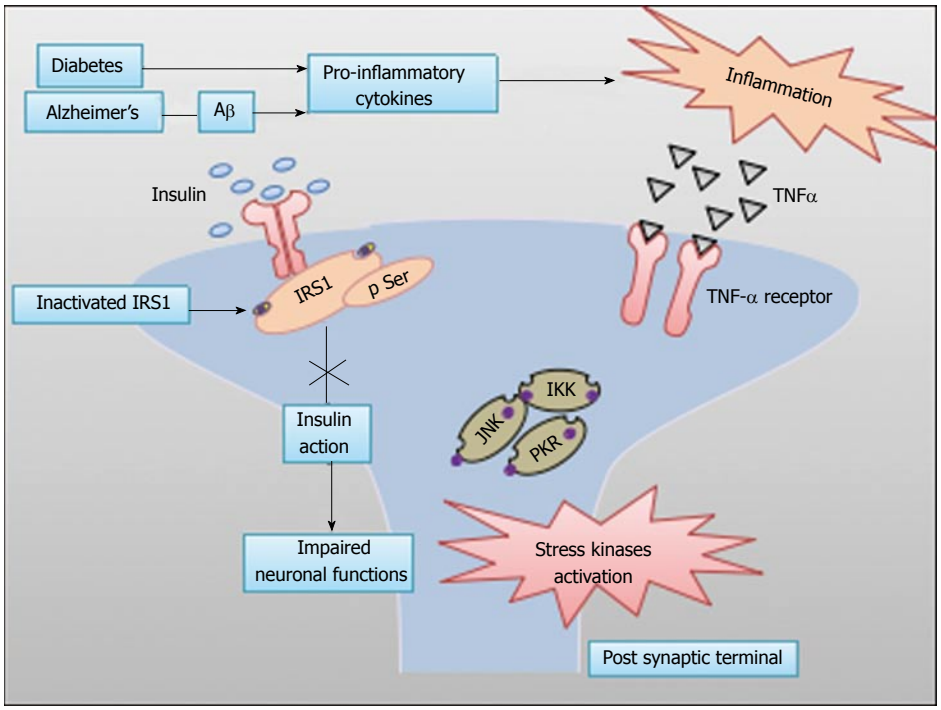

Figure 6 Diagrammatic representation of insulin signal dysfunction in Alzheimer's disease and diabetes mellitus *via* common inflammatory cascade. Diabetes and AD lead to production of pro-inflammatory cytokines in inflammatory response. These stress kinases inhibit IRs1, an adaptor protein for insulin receptor signaling and result into defective insulin signaling in brain. Aβ: Amyloid beta; IRs: Insulin receptors; JNK: c-Jun N-terminal kinases.

are major stress kinases which are common regulatory nodes between inflammation and metabolism[174,175]. Since insulin signaling contributes to normal functioning of neurons, any inflammation mediated alteration in these, results into defective neuronal function[95,176,177]. These evidences suggest that there is a common mechanistic pathway adopted by peripheral IR in T2D as well as impaired brain insulin signaling in AD.

OXIDATIVE STRESS: A COMMON BURDEN IN AD AND DM

Normal body physiology tends to maintain a balance between production of ROS and body's antioxidant defense system and any sort of imbalance altering this dynamic system leads to onset of metabolic disorder with cognitive dysfunction[178]. Hydrogen peroxide, hydroxyl radical, superoxide ion and singlet oxygen are such reactive species which are abundantly produced in cellular respiration cycles and have very short half life[179]. It is known that diabetic patients have more oxidative cellular environment as compared to healthy ones[180-182]. Hyperglycemic condition has proportionality with sorbitol production which reduces NADPH, a cofactor for GSH production and hence decreases antioxidant levels in the body[183-185]. One more prevalent mechanism of diabetes contributing towards ROS is insurgence of advanced glycation end products (AGEs) production[183,184,186], which binds to cell surface receptors, *i.e.*, receptor for advanced glycation end roducts (RAGEs). RAGEs-AGEs interaction leads to ROS production *via* NADPH oxidase system which in turn activates Ras-MAPK pathway and ultimately nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation[184,187]. Hyperglycemia also leads to flux of glucose or FFA into blood which turns hexosamine pathway on[188] for further ROS production[189]. Elevated levels of FFA have an adverse effect on mitochondrial functioning and uncouple oxidative phosphorylation to contribute in ROS production[190,191]. ROS production worsens the status of insulin signaling and stress pathways which lead to further ROS production to turn a vicious cycle on.

High polyunsaturated fatty acid proportion with GSH content leave neurons vulnerable and make them prone to free radical attack[192]. A noticeable increase in lipid peroxidation was observed in brain of AD patients[193-195]. Oxidative stress and Aβ aggregation has both way relationships controlling each other's turnover. Oxidative stress channels regulate Aβ dynamicity from non-aggregated form to aggregated form[196]. Aggregated Aβ acts like a source of free radical production and lipid peroxidation[197] to drive brain towards neurodegeneration.

MITOCHONDRIAL VULNERABILITY IN CASE OF AD AND DM

Mitochondria, a result of 1.5 billion years of obligate endosymbiotic co-evolution is a sub-cellular niche to take care of cell survival as well as programmed cell death[198]. Several decades of research has establis-

hed that fission-fusion dynamicity of mitochondria is critical in neurodegeneration[198]. As the brain is offered with limited capacity of glycolysis, neuronal cells are highly dependent on aerobic oxidative phosphorylation for energy production which is an electron transfer event from lower redox potential to higher redox potential[199-202]. Although, this electron chain transfer process is very efficient, still some ROS are produced which leads to oxidation of mitochondrial DNA, lipids and proteins further contributing to mitochondrial dysfunction which is a prominent feature of AD[181,203].

Substantial data from diabetic patients and animal model systems revealed that brain faces several structural and functional deficits. Functional impairment of mitochondria leads to neurodegeneration and loss of control over neuronal metabolism. A study reflected that there is a significant decrease in coenzyme Q levels in diabetic animals which represents a marked deficit in antioxidant defense system[204]. There are reports which are directly linking impairment in glucose utilization with mitochondrial dysfunction and metabolic disturbances[205-208]. In 2003, clear evidence of oxidative phosphorylation uncoupling was found in rat model of T2D[209]. Mitochondrial capacity of Ca^{2+} accumulation was also found to decrease in case of diabetes which is a favorable environment for mitochondrial permeability transition (MPT) opening and ultimately leads to cell death[210,211].

AD animal models as well as human studies suggested that AD pathology leads to mitochondrial dysfunction and ROS production. Some crucial molecules such as Aβ binding alcohol dehydrogenase are reported to aid to AD pathology by mediating Aβ induced cell death *via* mitochondrial channel[209,212]. In some reports it is mentioned that one of the insulin degrading enzymes isoform, a well established regulator of Aβ dynamicity targets mitochondria and interfere with its normal functioning[213]. Aβ is also found to be a good inhibitor of respiratory chain complex and thus leads to marked decrease in cellular ATP levels[214,215]. Importantly, Aβ 40 and Aβ 25-35 contribute in uncoupling of oxidative phosphorylation and impair respiratory chain as well as MPT opening[204,210,211]. Moreover Aβ induces H_2O_2 production which is rescued by CoQ10, a key enzyme of electron transport chain[216]. Various tri-carboxylic acid (TCA) cycle enzymes such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and ATP citrate lyase were also found to be dysregulated in case of AD[217].

Mitochondrial morphology was found to be altered with some functional loss in neurodegenerative disorders such as AD[218-221]. In brief it can be mentioned that a small metabolic compromise is sufficient to trigger a cascade and disrupt normal mitochondrial function which plays a vital role in neuronal survival, growth and plasticity.

THERAPEUTIC OPPORTUNITIES

Sedentary life style, dietary changes and genetic predisposition are conspired forces responsible for worldwide epidemic of metabolic and aging syndrome. Discovered molecular trajectories from T2D to T3D gained experimental momentum for new therapeutic interventions. Elucidating role of anti-diabetic drug for the treatment of AD translated the disease information and added new armaments to the arsenal of putative therapies. It is unquestionable issue that both of these disorders share common pathologies including glucose metabolism defects, mitochondrial dysfunction, oxidative stress and abnormal deposition of amyloidogenic proteins[55]. The reason why insulin got this recognition under frontier's of Alzheimer research is that its high level in CNS revealed its own crucial role in learning, memory, cognition and synaptic plasticity[222]. Although, brain has potential pyramidal neurons involved in synthesis and secretion of insulin, majority of brain insulin is replenished by peripheral source from pancreatic β cells transported through blood across BBB[223].

There are some well known potential oral drugs [such as biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), and dipeptidyl peptidase-Ⅳ (DPP-Ⅳ) inhibitors], injections (*e.g.*, insulin and GLP-1 analogs), and some other molecules like glucokinase activators, amylin analogs, D2-dopamine agonists, bile acid chelators, and sodium/glucose-linked transporter-2 inhibitors *etc.*, established for T2D. Most of the anti-diabetic drugs act through the mechanism of maintenance of plasma glucose level, regulation of inflammatory cascades and establishing the balance between ROS and antioxidants. We will briefly provide an overview of experimental and clinical trials of some anti-diabetic drugs which are being tested in patients with AD and with low to moderate mild cognitive impairment.

Metformin

Metformin, a well known biguanide anti-diabetic drug is used to reduce IR. It sensitizes liver and skeletal muscle cell *via* AMP kinase cascade[224,225]. Brain is most vulnerable vital organ for oxidative stress, because of high oxidative metabolism rate and limited antioxidant level. Under oxidative stress mitochondrial permeability pores open up to release cytochrome c and trigger apoptotic cascade. Metformin is reported to inhibit opening of these permeability pores in ectoposide-induced cell death model to inhibit apoptotic cascade[226]. Metformin is also involved in neurogenesis by activation of protein kinase C-CREB binding pathway (PKC-CBP) pathway in neuronal cell culture study, in human and rodent model system[227]. In neuronal cell lines (neuro2A), metformin promotes insulin action and attenuates molecular and pathological features observed in AD. Metformin treatment was found to reduce the risk of dementia in human aged subjects[228]. AD patients taking calcium in diet supplemented with metformin were found to have better cognitive performance[229]. Thus these evidences support the fact that metformin is not only a known anti-diabetic agent

but also an effective neuroprotective molecule.

Sulphonylurea

SUs is a class of anti-diabetic drugs which are used as mono or combined therapy to increase insulin secretion by enhancing pro-insulin level *via* voltage gated calcium channel but the actual mechanistic target is still under investigation[230]. SUs limits liver glucose production and decreases insulin clearance by liver. Glipizide and Glyburide (glibenclamide) are the main SUs compounds which are investigated for memory and cognition in diabetic patients.

Experimental and clinical studies

In case of diabetes and AD, PI3K/mTOR is found to be aberrantly activated. Glyburide and glipizide are reported to have properties of mTOR antagonist[231] but their efficacy to recover AD patients is yet to be determined. Inflammosomes are involved in the secretion of proinflammatory cytokines that results in inflammation and associates it to AD. Along with inhibiting mTOR pathway, gliburide is found to inhibit inflammosome and thus brain inflammation[232]. Exalto *et al*[230] reported that SUs treated T2D patients shows improved AD type dementia symptoms but the precise mechanism is still unknown.

DM patients treated with glipizide are reported to have better learning efficiency[233]. Some recent studies show that there is no alteration in the development of AD in population using SUs in long term[234]. Metformin and SUs in combination are reported to reduce the risk of dementia upto 35% in a prospective cohort study[228].

Intranasal insulin

Intranasal administration of insulin is reported to attenuate reduced insulin signaling in AD[235]. Importantly, intranasal insulin does not adversely affect blood insulin or glucose levels.

Experimental and clinical studies

It is evident that AD patients have low insulin level and brain insulin resistant state which leads to impaired energy metabolism of neurons and make them vulnerable for survival. Insulin has been reported with its anti-amyloidogenic effect in human neuronal cell lines[236]. Some reports have shown that Aβ induced neuronal IR is attenuated by insulin treatment[237].

In a study it is found that 20 IU insulin twice a day over a period of 21 d in early AD or MCI subject's helps to retain verbal information more effectively[30]. In 2006 Reger *et al*[30] showed that 10 IU intranasal insulin improves cognition in APOE4 AD/MCI subjects.

TZDs

TZDs (also represented as glitazones) are a potential class of drug used for T2D which includes rosiglitazone (avandia), pioglitazone (actos) and troglitazone (rezulin). Mechanism of this group lies in activation of peroxisome proliferator-activated receptors by mimicking as a potential agonist of it and involved in transcription of lipid and glucose metabolism genes[238,239]. Since TZDs are anti-amyloidogenic and anti-inflammatory compounds with insulin sensitizing role, these delay neurodegeneration[240]. It also improves glycemic control in diabetic patients by inhibiting hepatic gluconeogenesis. Moreover, TZDs (mainly Troglitazone) are supposed to have their involvement in rescuing memory loss and decreasing plasma Aβ 40 and Aβ 42 levels[241,242] but again it needs to be investigated further.

Experimental and clinical studies

Rosiglitazone is reported to attenuate neuronal IR induced by Aβ oligomers[237]. Pioglitazone is found to improve cognitive performance in a rodent dementia model induced by intracerebroventricular (ICV) injection of streptozotocin[243].

In a randomized trial rosiglitazone (8 mg) is reported to improve cognitive function in mild to moderate AD patients (non APOE4 carrier[244]). In contrast, a recent phase III trial of the same drug has failed to show similar effects in AD subjects[245]. Moreover, long term use of TZDs, in general has no effect on risk of AD development[234].

Glucagon like peptide 1

Glucagon like peptide 1 (GLP1) analogs are "incretin mimetics", used to treat T2D. Exenatide, a 39 amino acid long peptide is analogous to human GLP1 which stimulates insulin secretion in a glucose dependent fashion. In brain these analogues bind tor GLP receptors and mediate various functions like suppression of glucagon production, slow down gastric emptying, increase satiety and reduce food intake with lower risk of hypoglycemia.

Experimental and clinical studies

In an animal study, GLP1 is reported to protect neurons from oxidative stress with reduced apoptosis, plaque formation and inflammatory response. Moreover, it strengthens synaptic plasticity in AD mouse brain l[246]. It is shown to improve spatial memory in transgenic AD mice model[247]. Liraglutide and lixisenatide are GLP1 receptor agonists which are reported to activate cAMP in the brain and induce neurogenesis[248]. In addition, liraglutide attenuates memory impairments in a mouse model of AD[249]. Subcutaneous administration of liraglutide is reported to restore both peripheral and brain insulin sensitivity and ameliorates tau hyperphosphorylation in rat model of T2D[250]. Clinical research on the effect of liraglutide on AD patients is still going to evaluate the changes in cognition using a neuropsychological test battery[251].

DPP IV inhibitors: Oral hypoglyceimic

DPP-IV, pharmacological inhibitors are oral hypoglycemic. These compounds reduce blood glucose levels by increasing incretin (GLP-1 and GIP levels) and attenuating glucagon effects. Sitagliptin, Vildagliptin,

Saxagliptin, Linagliptin, Teneligliptin, Gemigliptin and Dutogliptin are major members of gliptins, out of which Dutogliptin is under Phase Ⅲ clinical trial[252]. Effect of sitagliptin administration is studied double transgenic mice model of AD and reported to significantly delay AD pathology including amyloid deposition and taupathies[253].

Insulin and oral anti-diabetics: A combined therapy

Combination of insulin and other oral anti-diabetic drugs are reported to lower neuritic plaque density by 20% in AD brains[253]. Metformin in combination with rosiglitazone or glyburide is reported to improve working memory very significantly[253]. In a prospective cohort study, metformin and SUs are reported to reduce risk of dementia by 35%[228]. Although, a number of anti-diabetic drugs are reported to improve cognitive effect, it is still not well understood whether these effects are due to glucose lowering effects or adopt different pathways of neuroprotection. A broad range of anti diabetic therapies are undergoing clinical trials including those involving stimulation of the pancreatic beta-cell with the gut-derived insulinotropic hormones (incretins), GIP and GLP-1[254]. Some drugs have good glycemic control but have no history to improve cognitive functions[255]. In a study diabetes patients were maintained at normoglycemia over 3 mo but no significant improvement in cognitive performance was observed[256]. Other than glycemic control, anti-diabetic drugs improve cognitive function. Although various clinical trials are underway to evaluate the role of anti-diabetic drugs in treatment of neurodegenerative disorders such as dementia and AD but the search is still not over.

CONCLUSION

This review provides a synopsis in which a metabolic disturbance becomes indispensible for life. This is a talk of a metabolic problem which emerges as a molecular signal defect and takes a form of syndrome with multiple complications. Spotlighted player, insulin draws a trajectory from diabetes to AD with multiple divergence and convergence.

AD and DM are two devastating syndromes with complex molecular interplay. Evidences of their shared molecular and biochemical footprints shed light on.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Aditya Sunkaria for his advice and support.

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